PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PCT 21406Y	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/US04/20752	International filing date *(day/month/year)* 25 June 2004 (25.06.2004)	Priority date *(day/month/year)* 01 July 2003 (01.07.2003)
International Patent Classification (IPC) or national classification and IPC IPC(7): C07D 235/04, 235/12, 253/26, 235/28, 487/04; A61K 31/4184, 31/4188; A61P 27/06 and US Cl.: 548/ 306.4, 307.1, 309.4; 544/184, 236, 256, 350; 514/394, 395, 243, 248, 249, 262		
Applicant MERCK & CO., INC.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☑ *(sent to the applicant and to the International Bureau)* a total of 7 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s))
      ____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
31 January 2005 (31.01.2005)	01 March 2005 (01.03.2005)
Name and mailing address of the IPEA/ US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Venkataraman Balasubramanian Telephone No. (571) 272-1600

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US04/20752

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))

☐ publication of the international application (under Rule 12.4)

☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☐ the description:
pages 1-62 as originally filed/furnished
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☒ the claims:
pages NONE as originally filed/furnished
pages* NONE as amended (together with any statement) under Article 19
pages* 63-69 received by this Authority on 31 January 2005 (31.01.2005)
pages* NONE received by this Authority on _____

☐ the drawings:
pages NONE as originally filed/furnished
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE
☒ the claims, Nos. NONE
☒ the drawings, sheets/figs NONE
☒ the sequence listing (*specify*): NONE
☒ any table(s) related to the sequence listing (*specify*): NONE

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing (*specify*): _____
☐ any table(s) related to the sequence listing (*specify*): _____

** If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US04/20752

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-15	YES
	Claims NONE	NO
Inventive Step (IS)	Claims 1-15	YES
	Claims NONE	NO
Industrial Applicability (IA)	Claims 1-15	YES
	Claims NONE	NO

2. Citations and Explanations (Rule 70.7)

Claims 1-15 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the compound, composition and method of use embraced in the amended claims 1-15. In view of the amendment to the originally presented claims 1-15, all prior art applied in the previous written opinion as to lack of novelty and inventive step, are deemed as obviated.

Claims 1-15 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry as therapeutic agents for treating eye diseases.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

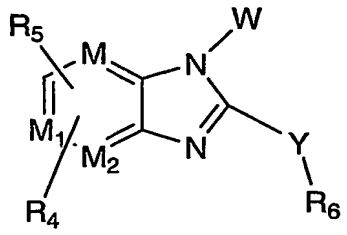
Continuation of:

V. 2. Citations and Explanations:

Case 21406Y PCT

WHAT IS CLAIMED IS:

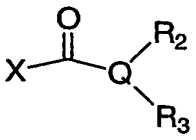
1. A compound of the structural formula I:



Formula I

or a pharmaceutically acceptable salt, enantiomer, diastereomer or mixture thereof:
wherein,

M, M1, and M2, independently are CH or N;

W represents  or $(CH_2)_nR_9$;

R represents hydrogen, or C_{1-6} alkyl;

X represents $-(CHR_7)_p-$, or a bond;

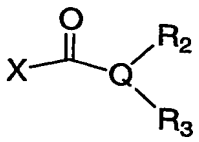
Y represents $-CO(CH_2)_n-$, $-SO_2-$, -O-, or -CH(OR')-;

R' represents hydrogen, C_{1-10} alkyl, $-(CH_2)_nC_{1-6}$ alkoxy, $-(CH_2)_nC_{3-8}$ cycloalkyl, $-(CH_2)_nC_{3-10}$ heterocyclyl, said alkyl, heterocyclyl, aryl or heteroaryl optionally substituted with 1-3 groups selected from R^a;

or, R' and R_6 taken together with the intervening N atom of CONR' of Y to form a 4-10 membered carbocyclic or heterocyclic ring optionally interrupted by 1-3 atoms of O, S, C(O) or NR, and optionally having 1-4 double bonds, and optionally substituted by 1-3 groups selected from R^a;

p is 0-2.

2. A compound according to claim 1 wherein M, M1, and M2 are all CH, or at least one of M, M1 or M2 is N.

3. A compound according to claim 2 wherein W represents  and X represents CHR_7.

4. A compound according to claim 2 wherein W represents $(CH_2)_nR_9$.

5. A compound according to claim 3 wherein Y is $-CO(CH_2)_n$, –or CH(OR) and Q is N or Ry.

6. A compound according to claim 5 wherein R_6 is C_{1-10} alkyl, $(CH_2)_nC_{6-10}$ aryl, $(CH_2)_nC_{5-10}$ heteroaryl, $(CH_2)_nC_{3-10}$ heterocyclyl, or $(CH_2)_nC_{3-8}$ cycloalkyl, said aryl, heteroaryl, heterocyclyl and alkyl optionally substituted with 1 to 3 groups of R^a, Y is $-CO(CH_2)_n$, Q is N, and R_2 and R_3 are independently selected from C_{1-10} alkyl, $(CH_2)_nC_{3-8}$ cycloalkyl, $-(CH_2)_n$-5~10-membered heteroaryl, $-(CH_2)_nC_{6-10}$ aryl, $-(CH_2)_n$-3~10-membered heterocyclyl, and C_{1-6} alkylOH said cycloalkyl, aryl, heteroaryl, heterocyclyl and alkyl optionally substituted with 1 to 3 groups of R^a.

7. A compound which is:
1-(1-Benzyl-6-methoxy-1*H*-benzimidazol-2-yl)-2,2-dimethylpropan-1-one,
1-(1-benzyl-5-methoxy-1*H*-benzimidazol-2-yl)-2,2-dimethylpropan-1-one,
1-(5-Methoxy-1*H*-benzimidazol-2-yl)-2,2-dimethylpropan-1-one,
Methyl [2-(2,2-dimethylpropanoyl)-6-methoxy-1*H*-benzimidazol-1-yl]acetate,
Methyl [2-(2,2-dimethylpropanoyl)-5-methoxy-1*H*-benzimidazol-1-yl]acetate,
[2-(2,2-Dimethylpropanoyl)-5-methoxy-1*H*-benzimidazol-1-yl]acetic acid,
2-[2-(2,2-Dimethylpropanoyl)-5-methoxy-1*H*-benzimidazol-1-yl]-*N*,*N*-bis(3-methylbutyl)acetamide,
1-(Diethoxymethyl)-6-methoxy-1*H*-benzimidazole,
1-(diethoxymethyl)-5-methoxy-1*H*-benzimidazole,
1-(6-Methoxy-1*H*-benzimidazol-2-yl)-2,2-dimethylpropan-1-one,
N,*N*-Dibutyl-2-[2-(2,2-dimethylpropanoyl)-5-methoxy-1*H*-benzimidazol-1-yl]acetamide,

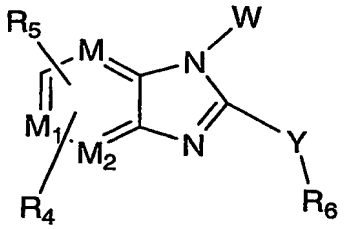
Case 21406Y PCT

2-[2-(2,2-Dimethylpropanoyl)-5-methoxy-1*H*-benzimidazol-1-yl]-*N*,*N*-diisobutylacetamide,

66

1-[5-methoxy-2-(2-phenylethyl)-1*H*-benzimidazol-1-yl]-3,3-dimethylbutan-2-one,
or a pharmaceutically acceptable salt, enantiomer, diastereomer or mixture thereof.

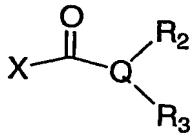
8. A method for treating ocular hypertension or glaucoma comprising administration to a patient in need of such treatment a therapeutically effective amount of a compound of structural formula I:



Formula I

or a pharmaceutically acceptable salt, enantiomer, diastereomer or mixture thereof:
wherein,

M, M1, and M2, independently are CH or N;

W represents  or $(CH_2)_nR_9$;

R represents hydrogen, or C_{1-6} alkyl;

X represents $-(CHR_7)_p-$, or a bond;

Y represents $-(CH_2)_r-$, $-CO(CH_2)_n-$, $-SO_2-$, -O-, -S-, -CH(OR')-, or CONR';

R' represents hydrogen, C_{1-10} alkyl, $-(CH_2)_nC_{1-6}$ alkoxy, $-(CH_2)_nC_{3-8}$ cycloalkyl, $-(CH_2)_nC_{3-10}$ heterocyclyl, said alkyl, heterocyclyl, aryl or heteroaryl optionally substituted with 1-3 groups selected from Ra;

or, R' and R_6 taken together with the intervening N atom of CONR' of Y to form a 4-10 membered carbocyclic or heterocyclic ring optionally interrupted by 1-3 atoms of O, S, C(O) or NR, and optionally

having 1-4 double bonds, and optionally substituted by 1-3 groups selected from R^a;

Q represents N, CR^Y, or O, wherein R_2 is absent when Q is O;

R^Y represents H, C_{1-10} alkyl, C_{1-6} alkylSR, $-(CH_2)_nO(CH_2)_mOR$, $-(CH_2)_nC_{1-6}$ alkoxy, $-(CH_2)_nC_{3-8}$ cycloalkyl, $-(CH_2)_nC_{3-10}$ heterocyclyl, $-(CH_2)_nC_{5-10}$ heteroaryl, $-N(R)_2$, -COOR, or $-(CH_2)_nC_{6-10}$ aryl, said alkyl, heterocyclyl, aryl or heteroaryl optionally substituted with 1-5 groups selected from R^a;

or, R_2-Q-R_3 form a 3-15 membered carbocyclic or heterocyclic ring or fused ring, optionally interrupted by 1-3 atoms of O, S, C(O) or NR, and optionally having 1-5 double bonds, and optionally substituted by 1-3 groups selected from R^a;

R_w represents H, C_{1-6} alkyl, $-C(O)C_{1-6}$ alkyl, $-C(O)OC_{1-6}$ alkyl, $-SO_2N(R)_2$, $-SO_2C_{1-6}$ alkyl, $-SO_2C_{6-10}$ aryl, NO_2, CN or $-C(O)N(R)_2$;

R_2 represents hydrogen, C_{1-10} alkyl, C_{1-6} alkylSR, $-(CH_2)_nO(CH_2)_mOR$, $-(CH_2)_nC_{1-6}$ alkoxy, $-(CH_2)_nC_{3-8}$ cycloalkyl, $-(CH_2)_nC_{3-10}$ heterocyclyl, $-(CH_2)_nC_{5-10}$ heteroaryl, $-N(R)_2$, -COOR, or $-(CH_2)_nC_{6-10}$ aryl, said alkyl, heterocyclyl, aryl or heteroaryl optionally substituted with 1-3 groups selected from R^a;

R_3 represents hydrogen, C_{1-10} alkyl, $-(CH_2)_nC_{3-8}$ cycloalkyl, $-(CH_2)_nC_{3-10}$ heterocyclyl, $-(CH_2)_nC_{5-10}$ heteroaryl, $-(CH_2)_nCOOR$, $-(CH_2)_nC_{6-10}$ aryl, $-(CH_2)_nNHR_8$, $-(CH_2)_nN(R)_2$, $-(CH_2)_nNHCOOR$, $-(CH_2)_nN(R_8)CO_2R$, $-(CH_2)_nN(R_8)COR$, $-(CH_2)_nNHCOR$, $-(CH_2)_nCONH(R_8)$, aryl, $-(CH_2)_nC_{1-6}$ alkoxy, CF_3, $-(CH_2)_nSO_2R$, $-(CH_2)_nSO_2N(R)_2$, $-(CH_2)_nCON(R)_2$, $-(CH_2)_nCONHC(R)_3$, $-(CH_2)_nCOR_8$, nitro, cyano or halogen, said alkyl, alkoxy, heterocyclyl, aryl or heteroaryl optionally substituted with 1-3 groups of R^a;

R_4 and R_5 independently represent hydrogen, C_{1-6} alkoxy, OH, $OCOR_3$, C_{1-6} alkyl, COOR, SO_3H, $O(CH_2)_nN(R)_2$, $O(CH_2)_nCO_2R$, C_{1-6} alkylcarbonyl, S(O)qRY, $(CH_2)_nOPO(OH)_2$, $O(CH_2)_nOPO(OH)_2$, $N(R)_2$, CF_3, nitro, cyano or halogen where said alkyl, and alkoxy, are optionally substituted with 1-7 groups of R^a;

Case 21406Y PCT

R_6 represents hydrogen, C_{1-10} alkyl, -$(CH_2)_nC_{6-10}$ aryl, -$(CH_2)_nC_{5-10}$ heteroaryl, (C_{6-10} aryl)O-, -$(CH_2)_nC_{3-10}$ heterocyclyl, -$(CH_2)_nC_{3-8}$ cycloalkyl, -COOR, -$C(O)CO_2R$, said aryl, heteroaryl,

heterocyclyl and alkyl optionally substituted with 1-3 groups selected from R^a;

R_7 represents hydrogen, C_{1-6} alkyl, -$(CH_2)_n$COOR or -$(CH_2)_nN(R)_2$,

R_8 represents -$(CH_2)_nC_{3-8}$ cycloalkyl, -$(CH_2)_n$ 3-10 heterocyclyl, C_{1-6} alkoxy or -$(CH_2)_nC_{5-10}$ heteroaryl, said heterocyclyl, aryl or heteroaryl optionally substituted with 1-3 groups selected from R^a;

R_9 represents C_{1-10} alkyl, -$(CH_2)_nC_{1-6}$ alkoxy, -$(CH_2)_nC_{3-8}$ cycloalkyl, -$(CH_2)_nC_{3-10}$ heterocyclyl, -$(CH_2)_nC_{6-10}$ aryl, -$(CH_2)_nC_{5-10}$ heteroaryl, or -N(R)2 wherein said alkyl, alkoxy, cycloalkyl, heterocyclyl, aryl, or heteroaryl are optionally substituted with 1-3 groups selected from R^a,

R^a represents F, Cl, Br, I, CF_3, $N(R)_2$, NO_2, CN, -COR_8, -$CONHR_8$, -$CON(R_8)_2$, -$O(CH_2)_n$COOR, -$NH(CH_2)_nOR$, -COOR, -OCF_3, -NHCOR, -SO_2R, -SO_2NR_2, -SR, (C_1-C_6 alkyl)O-, -$(CH_2)_nO(CH_2)_mOR$, -$(CH_2)_nC_{1-6}$ alkoxy, (aryl)O-, -OH, (C_1-C_6 alkyl)$S(O)_m$-, H_2N-C(=NH)-, (C_1-C_6 alkyl)C(O)-, (C_1-C_6 alkyl)OC(O)NH-, -(C_1-C_6 alkyl)$NR_w(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_1-C_6 alkyl)$O(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_1-C_6 alkyl)$S(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_1-C_6 alkyl)-C_{3-10} heterocyclyl-R_w, -$(CH_2)_n$-Z^1-$C(=Z^2)N(R)_2$, -(C_{2-6} alkenyl)$NR_w(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_{2-6} alkenyl)$O(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_{2-6} alkenyl)$S(CH_2)_nC_{3-10}$ heterocyclyl-R_w, -(C_{2-6} alkenyl)-C_{3-10} heterocyclyl-R_w, -(C_{2-6} alkenyl)-Z^1-$C(=Z^2)N(R)_2$, -$(CH_2)_nSO_2R$, -$(CH_2)_nSO_3H$, -$(CH_2)_nPO(OR)_2$, -$(CH_2)_nOPO(OR)_2$, -$O(CH_2)_nSO_2R$, -$O(CH_2)_nPO(OR)_2$,-O $(CH_2)_nOPO(OR)_2$, cyclohexyl, morpholinyl, piperidyl, pyrrolidinyl, thiophenyl, phenyl, pyridyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thienyl, furyl, isothiazolyl, C_{2-6} alkenyl, and C_1-C_{10} alkyl, said alkyl, alkenyl, alkoxy, phenyl, pyridyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, thienyl, furyl, and isothiazolyl optionally substituted with 1-3 groups selected from C_1-C_6 alkyl, COOR, SO_3H, OH, F, Cl, Br, I, and -$O(CH_2)_nCH(OH)CH_2SO_3H$;

Z^1 and Z^2 independently represents NR_w, O, CH_2, or S;

m is 0-3;
n is 0-3;
q is 0-2;

r is 0-6 and
p is 0-2.

71b

9. A method for treating macular edema, macular degeneration, increasing retinal and optic nerve head blood velocity, increasing retinal and optic nerve oxygen tension, and/or a neuroprotective effect comprising administration to a patient in need of such treatment a pharmaceutically effective amount of a compound of claim 8; or a pharmaceutically acceptable salt, enantiomer, diastereomer or mixture thereof.

10. A method of preventing repolarization or hyperpolarization of a mammalian cell containing potassium channel or a method of treating Alzheimer's Disease, depression, cognitive disorders, and/or arrhythmia disorders in a patient in need thereof comprising administering a pharmaceutically effective amount of a compound of Claim 8, or a pharmaceutically acceptable salt, enantiomer, diastereomer or mixture thereof.

11. A method of treating diabetes in a patient in need thereof comprising administering a pharmaceutically effective amount of a compound of claim 8, or a pharmaceutically acceptable salt, enantiomer, diastereomer or mixture thereof.

12. A composition comprising a compound of formula I of claim 1 and a pharmaceutically acceptable carrier.

13 The composition according to Claim 12 wherein the compound of formula I is applied as a topical formulation, said topical formulation administered as a solution or suspension and optionally containing xanthan gum or gellan gum.

14. A composition according to claim 13 wherein one or more of an active ingredient belonging to the group consisting of: □-adrenergic blocking agent, parasympatho-mimetic agent, sympathomimetic agent. carbonic anhydrase inhibitor, EP4 agonist, a prostaglandin or derivative thereof, hypotensive lipid, neuroprotectant, and/or 5-HT2 receptor agonist is optionally added.

15. A composition according to claim 14 wherein the □-adrenergic blocking agent is timolol, betaxolol, levobetaxolol, carteolol, or levobunolol; the parasympathomimetic agent is pilocarpine; the sympathomimetic agent is epinephrine, brimonidine, iopidine, clonidine, or para-aminoclonidine, the carbonic anhydrase inhibitor is dorzolamide, acetazolamide, metazolamide or

brinzolamide; the prostaglandin is latanoprost, travaprost, unoprostone, rescula, or S1033, the hypotensive lipid is lumigan, the neuroprotectant is eliprodil, R-eliprodil or memantine; and the 5-HT2 receptor agonist is 1-(2-aminopropyl)-3-methyl-1H-imdazol-6-ol fumarate or 2-(3-chloro-6-methoxy-indazol-1-yl)-1-methyl-ethylamine.